

Remarks on invariance of population distributions for systems with equivariant internal dynamics

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1 Introduction

There has been recent interest, particularly in the systems biology literature, in the study of symmetry invariances of responses of dynamical systems. The paper [1] obtained sufficient characterizations of symmetry invariance using a notion of equivariance, and this characterization was shown to be necessary as well as sufficient in [2]. Both [1] and [2] sketched how to extend the results to motile systems that explore space, so long as the “motor dynamics” depends only on an invariant response. Specifically, these results predicted that *E. coli* bacteria would produce scale-invariant searches, meaning that distributions of bacteria, even under non-uniform and time-varying chemoeffector fields, should be invariant under any rescaling of the input field. This prediction was subsequently experimentally verified in [3]. In this note, we remark that, for a velocity-jump Markov model, the PDE for the evolution of densities (or normalized concentrations) in time inherits the symmetry-invariance property from individual behaviors. Although not at all surprising, this provides further theoretical justification for passing from individual-based models to population predictions.

2 Symmetries and equivariances

We review the general setup in [1, 2]. Consider dynamical systems with inputs and outputs [4],

$$\dot{x} = f(x, u), \quad y = h(x, u). \quad (1)$$

The functions f , h describe respectively the dynamics and the read-out map.* Equation (1) is shorthand for

$$\frac{dx}{dt}(t) = f(x(t), u(t)), \quad y(t) = h(x(t), u(t)).$$

Here, $u = u(t)$ is a generally time-dependent input (stimulus, excitation) function, $x(t)$ is an n -dimensional vector of state variables, and $y(t)$ is the output (response, reporter) variable. States, inputs, and outputs are constrained to lie in particular subsets \mathbb{X} , \mathbb{U} , and \mathbb{Y} respectively, of Euclidean spaces $\mathbb{R}^n, \mathbb{R}^m, \mathbb{R}^q$.

We assume that for each piecewise-continuous input $u : [0, \infty) \rightarrow \mathbb{U}$, and each initial state $\xi \in \mathbb{X}$, there is a unique solution $x : [0, \infty) \rightarrow \mathbb{X}$ of (1) with initial condition $x(0) = \xi$, which we write

*The results in [2] were stated for h not directly dependent on u , but the theory is the same in the more general case of u -dependence, as was also remarked there.

as $\varphi(t, \xi, u)$, and we denote the corresponding output $y : [0, \infty) \rightarrow \mathbb{Y}$, given by $h(\varphi(t, \xi, u), u(t))$, as $\psi(t, \xi, u)$. We also assume that for each constant input $u(t) \equiv \bar{u}$, there is a unique solution $\bar{x} = \sigma(\bar{u})$ of the algebraic equation $f(\bar{x}, \bar{u}) = 0$. Often one also assumes that this steady state is globally asymptotically stable (GAS): it is Lyapunov stable and globally attracting for the system when the input is $u(t) \equiv \bar{u}$: $\lim_{t \rightarrow \infty} \varphi(t, \xi, u) = \sigma(\bar{u})$ for every initial condition $\xi \in \mathbb{X}$. The GAS property is not required for the results to follow, however.

If \mathbb{X} is an open set, or the closure of an open set, in \mathbb{R}^n , the system (1) is said to be *analytic* if f and h are real-analytic (can be expanded into locally convergent power series around each point) with respect to x , and *irreducible* if it is accessible and observable.

An accessible system is one for which the accessibility rank condition holds: $\mathcal{F}_{\text{LA}}(x_0) = \mathbb{R}^n$ for every $x_0 \in \mathbb{X}$, where \mathcal{F}_{LA} is the accessibility Lie algebra of the system. Intuitively, this means that no conservation laws restrict motions to proper submanifolds. For analytic systems, accessibility is equivalent to the property that the set of points reachable from any given state x has a nonempty interior; see a proof and more details in the textbook [4]. An observable system is one for which $\psi(t, x_0, u) = \psi(t, \widetilde{x}_0, u)$ for all u, t implies $x_0 = \widetilde{x}_0$. Intuitively, observability means that no pairs of distinct states can give rise to an identical temporal response to all possible inputs. For analytic input-affine systems, observability is equivalent to the property that any distinct two states can be separated by the observation space; see [4], Remark 6.4.2 for a proof and discussion. In the context of applications to biomolecular systems, analyticity and irreducibility are weak technical assumptions, often satisfied.

Adaptation, invariance, and equivariances

Definition 2.1 The system (1) *perfectly adapts to constant inputs* provided that the steady-state output $h(\sigma(\bar{u}), \bar{u})$ equals some fixed $y_0 \in \mathbb{Y}$, independently of the particular input value $\bar{u} \in \mathbb{U}$. \square

That is, the steady-state output value is independent of the actual value of the input, provided that the input is a constant (a step function).

Invariance will be defined relative to a set \mathcal{P} of continuous and onto input transformations $\pi : \mathbb{U} \rightarrow \mathbb{U}$. For each input $u(t)$ and $\pi \in \mathcal{P}$, we abuse notation and denote by “ πu ” (even if π is nonlinear) the function of time that equals $\pi(u(t))$ at time t . (The continuity assumption is only made in order to ensure that πu is a piecewise continuous function of time if u is. The onto-ness assumption, that is, $\pi\mathbb{U} = \mathbb{U}$, and can be weakened considerably: it is only used in the main theorem in order to prove that a system $\dot{x} = f(x, \pi u)$, $y = h(x, \pi u)$ is irreducible if the original system is irreducible, but far less than onto-ness is usually required for that.)

An example is *scale invariance*, in which $\mathbb{U} = \mathbb{R}_{>0}$ and $\mathcal{P} = \{u \mapsto pu, p \geq 0\}$. (Scale invariance is sometimes called “fold-change detection” (FCD), since the only changes that can be detected in a response are those due to different fold-changes in inputs.)

Definition 2.2 The system (1) has *response invariance to symmetries in \mathcal{P}* or, for short, is *\mathcal{P} -invariant* if

$$\psi(t, \sigma(\bar{u}), u) = \psi(t, \sigma(\pi\bar{u}), \pi u) \quad (2)$$

holds for all $t \geq 0$, all inputs $u = u(t)$, all constants \bar{u} , and all transformations $\pi \in \mathcal{P}$. \square

Under the assumption that the action of \mathcal{P} is transitive, i.e., for any two $\bar{u}, \bar{v} \in \mathbb{U}$, there is some π such that $\bar{v} = \pi\bar{u}$, \mathcal{P} -invariance implies perfect adaptation, because the outputs in (2) must coincide at time zero, and any two inputs can be mapped to each other.

Definition 2.3 Given a system (1) and a set of input transformations \mathcal{P} , a parametrized set of differentiable mappings $\{\rho_\pi : \mathbb{X} \rightarrow \mathbb{X}\}_{\pi \in \mathcal{P}}$ is a \mathcal{P} -equivariance family provided that, for each π :

$$f(\rho_\pi(x), \pi u) = (\rho_\pi)_*(x) f(x, u) \quad \text{and} \quad h(\rho_\pi(x), \pi u) = h(x, u) \quad (3)$$

for all $x \in \mathbb{X}$ and $u \in \mathbb{U}$, where $(\rho_\pi)_*$ denotes the Jacobian matrix of ρ_π . If (3) holds, the system is said to be ρ_π -equivariant under the input transformation π . \square

The first part of Equation (3) is a first order quasilinear partial differential equation on the n components of the vector function ρ_π , for each $u \in U$, and one may solve such equations, in principle, using the method of characteristics. The second part of Equation (3) is an additional algebraic constraint on these components. Observe that the verification of equivariance does not require the computation of solutions $\psi(t, \sigma(\pi \bar{u}), \pi u)$. We omit the subscript π when clear from the context.

The main result in [2] is as follows.

Theorem 1 *An analytic and irreducible system is \mathcal{P} -invariant if and only if there exists a \mathcal{P} -equivariance family.* \blacksquare

Remark 2.4 An interesting consequence of this theorem is that, if \mathcal{P} -invariance holds, then a stronger property holds as well, namely that

$$\psi(t, x, u) = \psi(t, \rho(x), \pi u)$$

is valid for all $t \geq 0$, all inputs u , all transformations $\pi \in \mathcal{P}$, and *every initial state* x (not necessarily a steady state). Another interesting fact, which follows from the proof of the theorem, is as follows. Suppose that we define a “weakly invariant” system as one for which there exists *some* constant \bar{u} such that (2) holds: $\psi(t, \sigma(\bar{u}), u) = \psi(t, \sigma(\pi \bar{u}), \pi u)$ for all inputs u and all $t \geq 0$ (instead of asking that this holds for every \bar{u}). Then, “weak invariance” implies the existence of an equivariance, and hence also invariance. The irreducibility property plays a subtle role in these facts. \square

3 Symmetry-invariant steering

We consider next a motile vehicle or organism which explores a space while measuring the “intensity” of an input cue (such as a chemoeffector or light). The sensed input at time t and position r is $U(t, r)$, where $r = r(t)$ is the current position of the vehicle. The current position $r(t)$ is derived from the output $y(t)$ of a system (1), through a computation that takes into account the dynamics of the motor and steering mechanisms.

Deterministic models for such mechanisms are sometimes appropriate, and one was described in [1, 2]. An easy argument for that deterministic model shows that, if y is invariant under symmetries in inputs, then positions $r(t)$ will be invariant under symmetry transformations on U .

It is often the case that a more accurate description is one in which the output $y(t)$ drives a stochastic, not a deterministic, steering mechanism: the subsystem producing the location $r(t)$ is subject to randomness.

An important instance of this is bacterial *E. coli* chemotaxis, where $y(t)$ represents a signal, the level of phosphorylated protein CheY, which serves to bias the random switches between tumbling and swimming (“run”) modes. Specifically, let us consider the Tu-Shimizu-Berg *E. coli* chemotaxis

model [5], which may be formulated, for realistic parameters and input levels, as follows: $\dot{m} = F_0(y)$, $y = h(m, u) = G(u/e^{\alpha m})$, where F_0 is a decreasing function which crosses zero at some value $y = y_0$ (and G is a suitable function whose precise form is immaterial for establishing symmetry). Letting $x := e^{\alpha m}$ and $F = \alpha F$, we may transform this system into a “nonlinear integral feedback” form,

$$\begin{aligned}\dot{x} &= x F(h(x, u)) \\ h(x, u) &= G(u/x) .\end{aligned}$$

For this system, homogeneity of $f(x, u) = xF(h(x, u))$ implies scale invariance, since the unique solution of the equivariance PDE is $\rho(x) = px$, for the scaling symmetry $u \mapsto pu$. Based on this verification of scale-invariant behavior, [1] predicted the invariance of distributions of bacteria locations under scalings of chemoattractant fields. This prediction was subsequently verified experimentally in [3] by means of molecular level analysis of intracellular signaling (FRET experiments) as well as measurements of swimming behavior at the level of individual cells and populations (in microfluidic environments).

A simple numerical simulation serves to illustrate the point. This simulation uses (with no change in parameters) the SPECS agent-based model for *E. coli* chemotaxis that was developed in [6].[†] In this simulation, cells are allowed to swim in a rectangular channel that is $2000\mu m$ long and $400\mu m$ wide, and data is collected in bins of size 20 (so, there are 100 bins along the long axis). The ligand gradient is stationary and linear (see below for boundary values) along the length and constant along the width. We simulated 1000 cells, all initially placed at the middle (at length 1000, i.e. bin 50), and plotted the marginal distributions (along the long axis on which the chemoattractant varies). Since their behavior is random, the averages of several (five) trials under each of the conditions are shown. These average histograms are plotted for the cell distribution at time $t = 500$. The blue and green histograms in Fig. 1 represent, respectively, results for cells pre-adapted to a concentration 250 (units are μM), and linear gradient $200 \dots 300$, and cells pre-adapted to a concentration 375, and linear gradient $300 \dots 450$ (a scale change by $p = 1.5$). As expected, the distributions are very similar. As a control, we also plotted the results of using, once again, a linear gradient $300 \dots 450$, but now pre-adapting cells to a concentration of 250. Since the initial state is not matched, there is no reason for invariance. Indeed, the resulting red histogram is very different from the previous ones.

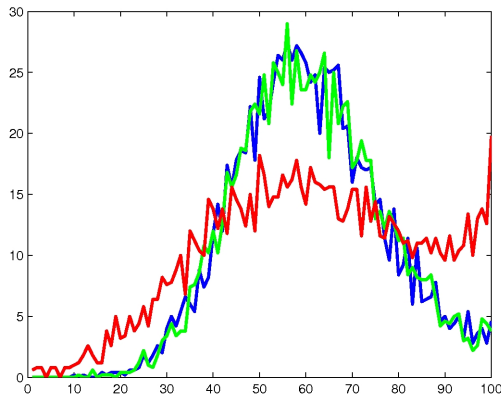


Figure 1: Simulations using SPECS code

[†]We thank Y. Tu for making this code available.

One may mathematically formalize probabilistic behavior, and show symmetry-invariance of search under randomness, in several possible ways. For instance, in [2] a simple result was presented on symmetry-invariance search based on pathwise equality of stochastic processes. We describe next a different approach, that employs the formalism of velocity-jump processes [7] with added internal dynamics [8].

We wish to model motions in a space \mathbb{R}^N (typically $N = 1, 2, 3$; and we assume for simplicity that motion can occur on the entire space) of individuals (bacteria, vehicles, etc) whose internal dynamics are described by the states x in (1) and which change velocities as a function of the output y . To avoid confusion with the variable x used for the internal state, we use the letter “ s ” to denote points in the space \mathbb{R}^N in which movement occurs. The input $u = u(t, s)$ represents an external signal present at time t in location s . The subset $V \subseteq \mathbb{R}^N$ denotes the space of possible velocities.

We assume that the system can instantaneously change orientations. (For *E. coli* bacteria this would mean that we are ignoring tumble durations.)

The concentration at time t of individuals present at time t in location s and having internal state x and velocity v is denoted by $c(t, s, v, x)$. We interpret $c(t, s, v, x) ds dv dx$ as the number of individuals located between s and $s + ds$, having velocity between v and $v + dv$, and whose internal state is between x and $x + dx$. Normalized by the total number of individuals, one may also think of c as a probability density, at each time t .

We assume that velocities change at random. The *times* at which velocities jump are controlled by a Poisson process with intensity $\lambda(y)$. Given that a jump in velocity occurs, *which* particular new velocity is picked is itself the result of a random choice; the kernel $T_y(v, v', y)$ gives the probability of a change in velocity from v' to v . Since T is a probability density, $\int_V T_y(v, v') dv = 1$ for every y . Notice that, just as with the jump instants, the kernel also depends on the state only through the output y .

Then the evolution (transport, Fokker-Planck, or forward Kolmogorov) equation for $c = c(t, s, v, x)$ is:

$$\frac{\partial c}{\partial t} + \nabla_s \cdot cv + \nabla_x \cdot cf = -\lambda(y)c + \int_V \lambda(y)T_y(v, v')c(t, s, v', x) dv' \quad (4)$$

where most arguments have been omitted for simplicity, but understood as holding for all (t, s, v, x) . (More generally, the right-hand side could be replaced by a more complicated discrete rate of change, if jumps are governed by a non-Poisson process.) The input at location s and time t is $U(t, s)$, and it appears in these equations through the vector field f in (1).

Sometimes it is useful to view (4) as a set of partial differential equations indexed and coupled by the velocities v . For example, when $N = 1$ and there is a constant speed $v_0 > 0$, $V = \{-v_0, v_0\}$ is a two-element set which provides the orientation of movement, $T_y(v, v') = 1$ (there is only one possible jump, namely a reversal of direction), and (4) describes a telegraph-type process: denoting $c^+(t, s, x) = c(t, s, v_0, x)$ and $c^-(t, s, x) = c(t, s, -v_0, x)$, (4) can then be thought of as set of coupled partial differential equations, one for $\partial c^+/\partial t$ and one for $\partial c^-/\partial t$:

$$\begin{aligned} \frac{\partial c^+}{\partial t} + v_0 \frac{\partial c^+}{\partial x} + \nabla_x \cdot f c^+ &= \lambda(y)[-c^+ + c^-] \\ \frac{\partial c^-}{\partial t} - v_0 \frac{\partial c^-}{\partial x} + \nabla_x \cdot f c^- &= \lambda(y)[c^+ - c^-]. \end{aligned}$$

The reference [8] discusses mathematical aspects of the PDE (4), which will not be discussed here. We focus, purely formally, on symmetry invariance.

Let us assume given π and an associated equivariance $\rho = \rho_\pi$, so that (3) holds:

$$f(\rho(x), \pi u) = \rho_*(x)f(x, u) \quad \text{and} \quad h(\rho(x), \pi u) = h(x, u)$$

for all $x \in \mathbb{X}$ and $u \in \mathbb{U}$, where ρ_* denotes the Jacobian matrix of ρ . We will also make the following assumption on the divergence of f :

$$(\nabla_x \cdot f)(\rho(x), \pi u) = (\nabla_x \cdot f)(x, u) \quad (5)$$

for all $x \in \mathbb{X}$ and $u \in \mathbb{U}$. This property is automatically satisfied for most of the examples treated in [2], since in these examples, which are for scale invariance $\pi u = pu$, ρ is a linear mapping. In general, if $\rho(x) = Rx$ for a matrix R , then the equivariance condition $f(Rx, \pi u) = Rf(x, u)$ implies, taking Jacobians, that $f_*(Rx, \pi u) = Rf_*(x, u)R^{-1}$. Since two similar matrices have the same trace, and $\nabla_x \cdot f$ is the trace of the Jacobian of f , it follows that (5) is valid.

Our main observation is that the same distribution of individuals will result if the input field U is replaced by πU , provided that the internal states are transformed by ρ . A precise statement is as follows.

Theorem 2 *Suppose that c satisfies (4) with respect to an input field U . Define*

$$\tilde{c}(t, s, v, x) = c(t, s, v, \rho^{-1}(x)).$$

Then \tilde{c} satisfies (4) with respect to the input field πU .

Proof. We start by writing all the arguments in (4) explicitly:

$$\begin{aligned} & \frac{\partial c}{\partial t}(t, s, v, x) + (\nabla_s \cdot \Gamma_1)(t, s, v, x) + (\nabla_x \cdot \Gamma_2)(t, s, v, x) \\ &= -\lambda(h(x, U(t, s)))c(t, s, v, x) \\ &+ \int_V \lambda(h(x, U(t, s)))T_{h(x, U(t, s))}(v, v')c(t, s, v', x) dv' \end{aligned}$$

where

$$\begin{aligned} \Gamma_1(t, s, v, x) &= c(t, s, v, x)v \\ \Gamma_2(t, s, v, x) &= c(t, s, v, x)f(x, U(t, s)). \end{aligned}$$

Since this equation must hold for all x , it holds also when $\rho^{-1}(x)$ is replaced for x , in other words it is also true that

$$\begin{aligned} & \frac{\partial c}{\partial t}(t, s, v, \rho^{-1}(x)) + (\nabla_s \cdot \Gamma_1)(t, s, v, \rho^{-1}(x)) + (\nabla_x \cdot \Gamma_2)(t, s, v, \rho^{-1}(x)) \\ &= -\lambda(h(\rho^{-1}(x), U(t, s)))c(t, s, v, \rho^{-1}(x)) \\ &+ \int_V \lambda(h(\rho^{-1}(x), U(t, s)))T_{h(\rho^{-1}(x), U(t, s))}(v, v')c(t, s, v', \rho^{-1}(x)) dv' \end{aligned}$$

for all t, s, v, x . From the definition of \tilde{c} and the property $h(\rho(x), \pi u) = h(x, u)$, which implies that $h(x, \pi u) = h(\rho^{-1}(x), u)$ for all u , we conclude that:

$$\begin{aligned} & \frac{\partial \tilde{c}}{\partial t}(t, s, v, x) + (\nabla_s \cdot \Gamma_1)(t, s, v, \rho^{-1}(x)) + (\nabla_x \cdot \Gamma_2)(t, s, v, \rho^{-1}(x)) \\ &= -\lambda(h(x, \pi U(t, s)))\tilde{c}(t, s, v, x) \\ &+ \int_V \lambda(h(x, \pi U(t, s)))T_{h(x, \pi U(t, s))}(v, v')\tilde{c}(t, s, v', x) dv'. \end{aligned}$$

It will follow that \tilde{c} is a solution of (4) with respect to the input field πU provided that we show:

$$\begin{aligned}(\nabla_s \cdot \Gamma_1)(t, s, v, \rho^{-1}(x)) &= (\nabla_s \cdot \tilde{\Gamma}_1)(t, s, v, x) \\ (\nabla_x \cdot \Gamma_2)(t, s, v, \rho^{-1}(x)) &= (\nabla_x \cdot \tilde{\Gamma}_2)(t, s, v, x),\end{aligned}$$

where

$$\begin{aligned}\tilde{\Gamma}_1(t, s, v, x) &= \tilde{c}(t, s, v, x)v \\ \tilde{\Gamma}_2(t, s, v, x) &= \tilde{c}(t, s, v, x)f(x, \pi U(t, s)).\end{aligned}$$

Since $\tilde{c}(t, s, v, x) = c(t, s, v, \rho^{-1}(x))$, the equality for ∇_s is clear. We are left to show the equality for ∇_x . We have, fixing t, s, v and letting $F(x) = f(x, U(t, s))$, $C(x) = c(t, s, v, x)$, $\tilde{F}(x) = f(x, \pi U(t, s))$, and $\tilde{C}(x) = \tilde{c}(t, s, v, x) = C(\rho^{-1}(x))$:

$$\begin{aligned}\nabla_x \cdot [\tilde{C}\tilde{F}](x) &= (\partial\tilde{C}/\partial x)(x)\tilde{F}(x) + \tilde{C}(x)(\nabla_x \cdot \tilde{F})(x) \\ &= (\partial C/\partial x)(\rho^{-1}(x))(\rho^{-1})_*(x)\tilde{F}(x) + C(\rho^{-1}(x))(\nabla_x \cdot \tilde{F})(x) \\ &= (\partial C/\partial x)(\rho^{-1}(x))[\rho_*(\rho^{-1}(x))]^{-1}\tilde{F}(x) + C(\rho^{-1}(x))(\nabla_x \cdot \tilde{F})(x) \\ &= (\partial C/\partial x)(\rho^{-1}(x))F(\rho^{-1}(x)) + C(\rho^{-1}(x))(\nabla_x \cdot F)(\rho^{-1}(x)) \\ &= \nabla_x \cdot [CF](\rho^{-1}(x)),\end{aligned}$$

where we have used that $f(\rho(x), \pi u) = \rho_*(x)f(x, u)$, and thus also $\tilde{F}(x) = \rho_*(\rho^{-1}(x))F(\rho^{-1}(x))$, as well as the divergence property (5). \blacksquare

In applications, one is often interested in the distribution of positions irrespective of internal states x and velocities v :

$$Q(t, s) = \int_{\mathbb{X}} \int_V c(t, s, v, x) d\mu_{\mathbb{X}}(x) d\mu_V(v)$$

where $\mu_{\mathbb{X}}$ and μ_V denote appropriate measures on \mathbb{X} and V (and we assume that c is integrable). Take the density corresponding to πU , $\tilde{c}(t, s, v, x) = c(t, s, v, \rho^{-1}(x))$, and its marginal

$$\tilde{Q}(t, s) = \int_{\mathbb{X}} \int_V \tilde{c}(t, s, v, x) d\mu_{\mathbb{X}}(x) d\mu_V(v).$$

This is the same as $\int_{\mathbb{X}} \int_V c(t, s, v, x)r(x) d\mu_{\mathbb{X}}(x) d\mu_V(v)$, where $r(x) = 1/\det \rho_*(x)$. In the special (but usual in examples) case that ρ is linear, r is a constant, so $\tilde{Q}(t, s) = rQ(t, s)$. It follows that the normalized densities are equal:

$$\frac{\tilde{Q}(t, s)}{\int \tilde{Q}(t, \sigma) d\sigma} = \frac{Q(t, s)}{\int Q(t, \sigma) d\sigma}.$$

Alternatively, one could introduce a new measure $d\tilde{\mu}_{\mathbb{X}}(x) = r(x)\mu_{\mathbb{X}}$, and define \tilde{Q} using this new measure, for all times t and space positions s , so that $Q(t, s) = \tilde{Q}(t, s)$.

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